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Example 3: CO_2 Leaf Extract of *Azadirachta indica*

[0282] One KG of cleaned and matured *Azadirachta indica* leaves were taken and dried under the shade to reduce moisture content to less than 12%. It was ensured that the powder contains moisture less than 12%. Such dried herb was powdered in particle size below 0.42 mm and then subjected to SCO_2 extraction at a pressure varying between 80 Bar (80 kg/cm^2) and 350 Bar (350 kg/cm^2) at a temperature ranging between 31° C. and 45° C. The CO_2 was passed through the herb for a period of 2-3 hours depending upon the size of the extractors and the quantity of herb loaded into the extractor at a time. The quantity of CO_2 to be pumped through the herb varies between 10 kg of CO_2/kg of herb to 40 kg of CO_2/kg of herb depending upon the solubility of lipophilic compounds present in the herb. The CO_2 carried extractives were collected from the separator where the pressure of CO_2 was reduced to a pressure varying between 40 Bar to 65 Bar and temperature between 10° C. to 30° C. to separate the solute (extract) and the CO_2. The extract thus obtained contains the temperature sensitive ingredients present in the herb and the other lipophilic soluble compounds. The extract thus obtained is Extract A.

[0283] Residual powder after isolating Extract 'A' was subjected to extraction using mixture of CO_2 and ethyl alcohol in proportion of 90 to 97% of Supercritical CO_2 and 3 to 10% of ethyl alcohol. The extraction was carried out at the pressure ranging between 80 Bar and 300 Bar and temperature ranging between 31° C. to 45° C. The quantity of solvent pumped (CO_2+Ethanol) varies between 10 kg/kg of herbs to 40 kg/kg of herbs. The solute (extract) and ethanol were separated from the CO_2 on reducing the solvent pressure between 40 Bar and 65 Bar and temperature between 10° C. to 30° C. The ethyl alcohol laced with extract was collected from the separator. The mixture was then subjected to vacuum distillation (27 to 28.5 inch of Hg) keeping temperature below 45° C., for separating the ethyl alcohol completely from the solute (extract), which was named as Extract B.

[0284] Residual solvent (ethanol): less than 1000 ppm

[0285] Both the extracts extract 'A' and extract 'B' were combined to obtain Extract C.

[0286] Yield: 2.5-5%

Example 4: Water Extract of *Azadirachta indica*

[0287] The herb powder of *Azadirachta indica* leaves (1 KG) was subjected to water extraction to obtain the water-soluble extractives in a paste form. The extract thus obtained was dried in tray dryers/vacuum dryer or in spray dryer to obtain free flowing powder extract. This extract is termed as water extract.

[0288] Yield: 5:1%.

Example 5: Standardization of the CO_2 Extract

[0289] The standardization of the CO_2 extract was carried out using HPLC. C18 column (4 mm×250 mm×5 μm) was used. The sample was prepared in methanol and the mobile phase was methanol and water. A gradient program sequence was used where the run time was 60 minutes and the flowrate were 1 ml/min. The extract obtained is having a minimum of nimbolide in an amount of 3 mg/gm, nimbin in an amount of 130 μg/gm and salinin in an amount of 200 μg/gm.

Example 6: Therapeutically Effective Formulations for Oral Use

[0290] Formulation 1.

[0291] SCO_2 *Azadirachta indica* leaf extract: 75 mg (with minimum 0.22 mg nimbolide; 9.75 μg nimbin and salinin 15 μg); antioxidants such as Vitamin E (tocopherols) or Rosemary (*Rosemarinus officinalis*) CO_2 extract containing minimum 6% carnosic acid: 10 mg and sesame oil: 415 mg; this formulation was filled in a soft gel capsule of 500 mg.

[0292] This capsule can be administered to the patient 2-4 times a day (total 150-300 mg of Neem leaf extract per day as an active drug).

[0293] Formulation 2.

[0294] SCO_2 *Azadirachta indica* leaf extract: 50 mg (with minimum 0.15 mg nimbolide; 6.5 μg nimbin and salinin 10 μg), 582 mg dextrin/malto-dextrin or other carrier (e.g., di-calcium phosphate or any other pharmaceutical grade carrier); and 18 mg aerated or fumed silica.

[0295] A free-flowing powder was prepared and encapsulated in suitable size of hard gelatin or vegetarian capsule available in the market. This formulation can be administered 3-4 times a day to get a therapeutic dose of 150-300 mg Neem leaf CO_2 extract.

[0296] Formulation 3.

[0297] SCO_2 *Azadirachta indica* leaf extract: 50 mg (with minimum 0.15 mg nimbolide; 6.5 μg nimbin and salinin 10 μg), 582 mg of water extract obtained from Neem leaf and 18 mg aerated or fumed silica.

[0298] A free-flowing powder was prepared and encapsulated in suitable size of hard gelatin or vegetarian capsule available in the market. This formulation can be administered 3-4 times a day to get a therapeutic dose of 150-300 mg Neem leaf CO_2 extract.

[0299] Formulation 4.

[0300] Mouthwash formulation containing SCO_2 *Azadirachta indica* leaf extract: 2.28 g (with minimum nimbolide: 7.2 mg; nimbin: 296.4 μg and salinin 456 μg), Peppermint (*Mentha piperita*) oil: 13.81 g, Spearmint (*Mentha spicata*) oil: 9.26 g, Clove Bud (*Syzigium aromaticum*) CO_2 oil: 3.98 g, Tween 80: 20.68 g. 1.25 g of the said blend was diluted in 98.75 g in Base. The base contains water: 73.5 g, Aloe Vera water (200×): 10 g, sorbitol: 10 g, glycerin: 5.9 g, ascorbic acid: 0.5 g, potassium porbate: 0.1 g.